Sex difference in the immunogenicity of the quadrivalent Human Papilloma Virus vaccine: Systematic review and meta-analysis

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Abstract: Background: Immunological differences between males and females in response to viral vaccines are well known. This the first review to examine them for the Human Papilloma Virus. Methods: We conducted a systematic review and meta-analysis of the immunogenicity of the Quadrivalent Human Papilloma Virus Vaccine qHPVV. We searched Medline, Embase, and CENTRAL for trials published until September 17, 2019. Inclusion criteria were 3-doses and reporting geometric mean titers (GMTs). We performed random-effects meta-analyses and meta-regression separated by age group and sex. Results: Our search yielded 1809 unique studies. 334 full texts were screened and data from 18 studies were extracted. Females had higher pooled geometric mean titers than males in all age groups. Log transformed GMTs in male children (<16) years were: against HPV6: $6 \cdot 62$ (95% CI $6 \cdot 29$-$6 \cdot 94$; I2 = $86 \cdot 0$%), against HPV11: $7 \cdot 07$ (95% CI $6 \cdot 90$-$7 \cdot 23$; I2 = 63.1%), against HPV16: $8 \cdot 53$ (95% CI $8 \cdot 28$-$8 \cdot 78$; I2 = $73 \cdot 0$%), and against HPV18 $7 \cdot 21$ (95% CI $7 \cdot 08$-$7 \cdot 34$; I2 = $26 \cdot 4$%). In females: against HPV6 $7 \cdot 10$ (95% CI $6 \cdot 79$-$7 \cdot 41$; I2 = $96 \cdot 6$%), HPV11: $7 \cdot 32$ (95% CI $7 \cdot 15$-$7 \cdot 50$; I2 = $90 \cdot 6$%), HPV16: $8 \cdot 71$ (95% CI $8 \cdot 52$-$8 \cdot 91$; I2 = $90 \cdot 2$%), and HPV18 $7 \cdot 35$ (95% CI $7 \cdot 11$-$7 \cdot 58$; I2 = $92 \cdot 7$%). In the meta-regression, the sexual difference was significant for HPV6 (p = $0 \cdot 022$) with a similar tendency for HPV11 (p = $0 \cdot 066$) and HPV18 (p = $0 \cdot 079$). Immunogenicity was significantly higher in children (<16) than in adults (p < $0 \cdot 001$). Conclusion: Females have higher antibody titers against HPV after receiving the qHPVV than do males. The difference is bigger in low-risk HPV strains. Adjusting the doses and schedules for each sex should be explored further. Keywords: Antibody response; Cervical cancer; Human Papilloma Virus; Immunogenicity; Quadrivalent HPV vaccine; Sex difference.

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Review

Sex difference in the immunogenicity of the quadrivalent Human Papilloma Virus vaccine: Systematic review and meta-analysis

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ABSTRACT

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Results: Our search yielded 1809 unique studies. 334 full texts were screened and data from 18 studies were extracted. Females had higher pooled geometric mean titers than males in all age groups. Log transformed GMTs in male children (<16) years were: against HPV6: 6·62 (95% CI 6·29–6·94; I^2 = 86·0%), against HPV11: 7·07 (95% CI 6·90–7·23; I^2 = 63.1%), against HPV16: 8·53 (95% CI 8·28–8·78; I^2 = 73·0%), and against HPV18 7·21 (95% CI 7·08–7·34; I^2 = 26·4%). In females: against HPV6 7·10 (95% CI 6·79–7·41; I^2 = 96·6%), HPV11: 7·32 (95% CI 7·15–7·50; I^2 = 90·6%), HPV16: 8·71 (95% CI 8·52–8·91; I^2 = 90·2%), and HPV18 7·35 (95% CI 7·11–7·58; I^2 = 92·7%). In the meta-regression, the sexual difference was significant for HPV6 (p = 0·022) with a similar tendency for HPV11 (p = 0·066) and HPV18 (p = 0·079). Immunogenicity was significantly higher in children (<16) than in adults (p < 0·001).
Conclusion: Females have higher antibody titers against HPV after receiving the qHPVV than do males. The difference is bigger in low-risk HPV strains. Adjusting the doses and schedules for each sex should be explored further.

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1. Introduction

Human Papilloma Virus (HPV) infection remains the most commonly diagnosed sexually transmitted infection worldwide [1]. There are more than 100 HPV virus types, which can be separated into two different risk groups depending on the outcome of the infection. Infections with a low-risk HPV (LR), such as HPV 6 and 11, are mostly inconspicuous but can cause benign papilloma [2]. High-risk types (HR), on the other hand, are highly carcinogenic and cause oropharyngeal and anogenital cancers [2]. A substantial proportion of oropharyngeal, anal, penile, vaginal, and vulvar cancers, and practically all cervical cancers, are associated with HPV infection [3,4]. HPV-related cancers are less common in men, who suffer 0.8% incidence of penile carcinoma and 0.5% of anal cancer [5]. However, HPV DNA was detected in 42% of penile carcinomas, in up to 90% of anal carcinomas, and in 100% of condylomas, meaning that HPV infections can still be a major source of morbidity and mortality in this group [6,7]. Furthermore, HPV seems to be responsible for 20.6% of all oropharyngeal cancers worldwide, and up to 21.6% in North America [8,9].

Since it was approved for medical use by the FDA in 2006, the HPV vaccine has been an efficient preventive measure against HPV infections and related cancers [10]. As genital warts were associated with a high economic burden for many countries and with a high psychosocial burden for those afflicted, most countries opted for the quadrivalent vaccine [11]. Clinical trials proved that the quadrivalent HPV vaccine (qHPVV) is efficacious in preventing infection and dysplasia caused by HPV 6, 11, 16, and 18 [12,13]. Most of these trials were conducted on women, but some included men as well. However, there is a substantial body of evidence that the immunological response to foreign and self-antigens differs between males and females [14]. In fact, one of the most conserved sex differences in immunology is the difference in humoral immunity (i.e., antibody response) [14]. These sex-based immunological differences contribute to variations in the response to vaccines between males and females, with females showing greater vaccine efficacy than males [15]. Antibody responses to seasonal influenza, for example, are twice as high in women than in men [16]. This difference is particularly relevant for the HPV vaccine because females have higher titers of antibodies against natural HPV infections, and a larger proportion of females are seropositive (17.9% in females compared to7.9% in males) [17,18]. This sex difference with higher antibody responses in females was also observed in other sexually transmitted viral infections that can be prevented by vaccination, as hepatitis B [9,15,19].

Antibody responses remain the standard test for vaccine immunogenicity and the protection established by vaccines is largely mediated by antibodies [20,21]. We, therefore, reviewed and analyzed the immunogenicity of the qHPVV, and compared it across the two sexes and two age groups (younger or older than 16).

2. Methods

2.1. Search strategy and selection criteria

We searched library databases MEDLINE, EMBASE, and Cochrane and screened bibliographies of included articles. Additional references were screened according to the same selection process as those found in the primary search. We did not set any language restrictions or a time limit to dates of published articles. We conducted the literature search on April 18, 2018 and updated it on September 17, 2019.

To capture studies on the immunogenicity of the HPV vaccine, we developed the search terms: "Human Papillomavirus" or "HPV" plus "Vaccine" plus "randomised" or "randomized" or "controlled" plus "trial" or "follow up" or "cohort". We also assessed abstracts from relevant conferences.

Eligible studies had to be randomized controlled trials or controlled trials that assessed the immunogenicity of the qHPV vaccine. All participants had to be healthy and HPV-negative at the beginning of the study. We excluded studies on populations that include HIV positive patients, HBV positive patients, or patients with any other infectious disease. We only included studies that reported their results as the geometric mean titers (GMT) and the associated confidence interval and used a competitive Luminex-based immunoassay (cLIA) to assess the antibody level in the blood. The vaccine had to be administered in a 3-dose schedule over 6 months (one dose at month 0, 1, and 6 respectively) and GMT measured at the end of the sixth month. This outcome was used as the indicator for qHPVV immunogenicity. We included all age groups, but the results had to be reported separately for males and females to enable comparison between the sexes.

LA and VMH independently screened the studies and extracted the data using the online Covidence program [22]. The first screening phase was based on the titles and abstracts. We then assessed the full text of the relevant studies to reach a final decision about inclusion or exclusion. Disagreements were resolved by discussion. We extracted the relevant data into a standardized spreadsheet that included: funding, country, authors' affiliation, study methods, population characteristics, study design, baseline characteristics (age, sample size, and serostatus), and outcomes (GMTs at month 7).

2.2. Bias risk assessment

We assessed the quality of the included randomized controlled trials using the Cochrane risk of bias tool [23]. We assessed sequence generation, allocation concealment, blinding of participants and study personnel for all outcomes, blinding of outcome assessors for all outcomes, incomplete outcome data for all outcomes, and selective outcome reporting, and rated the studies as high, low, or unclear risk of bias.

2.3. Statistical analysis

We performed random-effects meta-analyses to assess the mean difference and 95% confidence intervals between log transformed GMTs for each virus (HPV 6, 11, 16,18) and sex separately, and for adults and children. We assessed heterogeneity between studies using I^2 statistics [24]. We performed meta-regressions on the results of the meta-analyses, including all studies per virus type, to assess the significance of the variables sex and age. We used STATA version 14 (StataCorp, Austin, USA) for all analyses.

2.4. Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and shared the final responsibility for the decision to submit for publication.

3. Results

Our search yielded 2915 studies. After removing duplicates, 1805 unique studies remained. 1475 were excluded through title and abstract screening because they were not relevant to the present study. The full texts of the remaining 334 studies were assessed and 316 were excluded (see flowchart in Fig. 1 for details). Through screening the bibliographies of the assessed full-text arti-

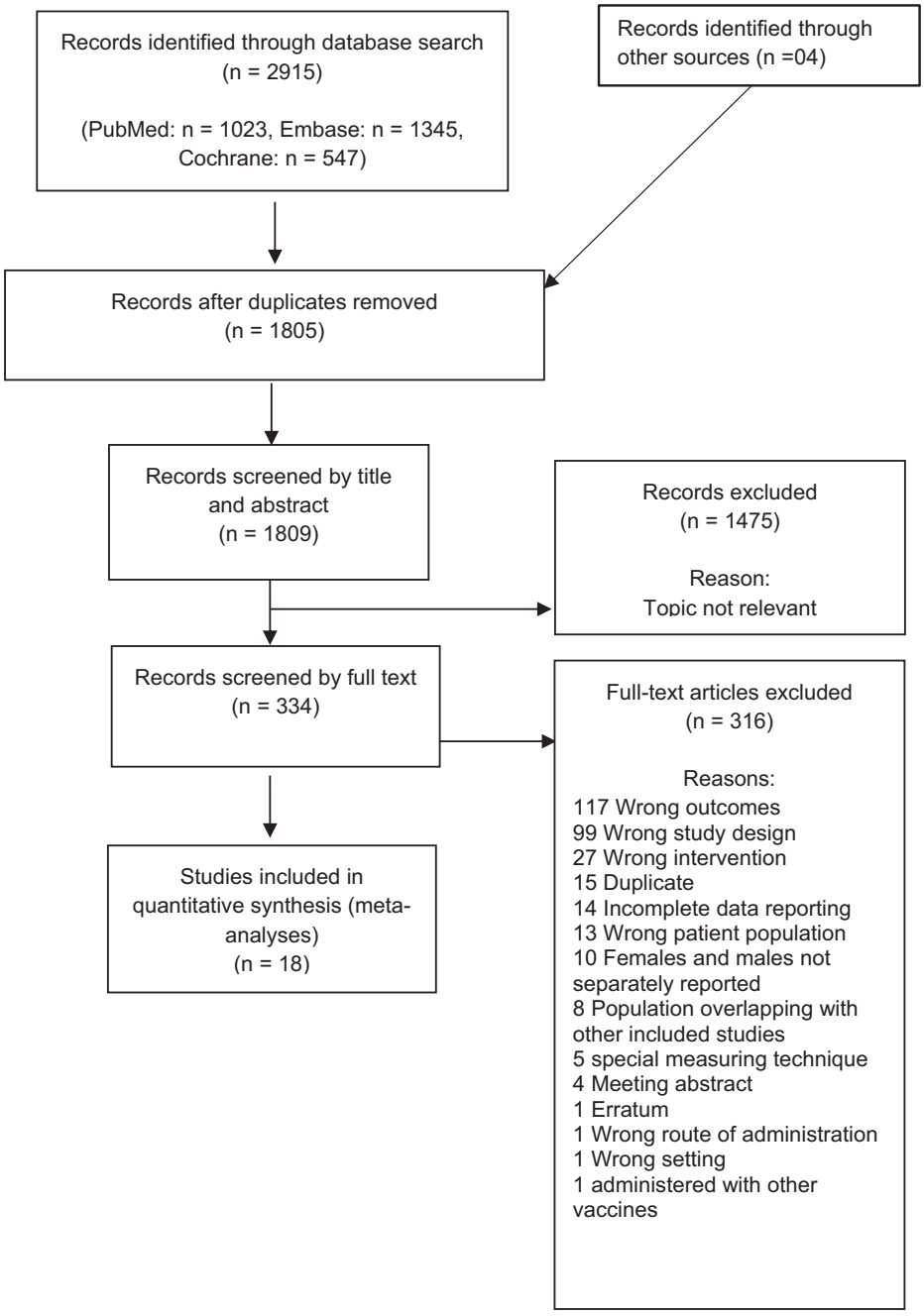

Fig. 1. Flow chart of studies showing inclusion and exclusion of studies at every review step, and reasons for exclusion.

cles, four additional articles were found. Eighteen studies, including three clinical trials and 15 randomized controlled trials, met our inclusion criteria. Included studies came from North and Latin America, Europe, Africa, and East Asia. Ten studies included female subjects only, six studies male subjects only, and two both female and male subjects. Ten studies were conducted on adults (>16 years old), five on young adolescents (<16 years old), and three on both age groups.

The estimated mean antibody-titers in adult women were based on eight studies that presented GMTs from competitive Luminex-based immunoassay testing with accompanying CIs in women older than 16 [25–32]. The pooled geometric mean titer estimate in women after qHPVV was as follows: 6·42 against HPV6 (95% CI 6·21–6·62; I^2 = 98·6%, p < 0·0001), 6·60 against HPV11 (95% CI 6·45–6·75; I^2 = 97·2%,p < 0·0001), 8·00 against HPV16 (95% CI 7·85–8·16; I^2 = 96·9%,p < 0·0001), and 6·42 against HPV18 (95% CI 6·21–6·63; I^2 = 98·3%,p < 0·0001). Five studies presented similar data on the GMTs in men older than 16 [33–37]. Accordingly, the pooled geometric mean titer estimate in men after qHPVV was as follows: 6·20 against HPV6 (95% CI 6·02–6·38; I^2 = 92·7%,p < 0·0001), 6·46 against HPV11 (95% CI 6·25–6·67; I^2 = 95·5%,p < 0·0001), 7·89 against HPV16 (95% CI 7·72–8·05; I^2 = 92·3%, p < 0·0001), and 6·20 against HPV18 (95% CI 5·96–6·44; I^2 = 94·7 %,p < 0·0001) Figure Supplementary Fig. S2, Supplementary Fig. S4, Supplementary Fig. S6 and Supplementary Fig. S8.

In children <16 years of age, nine studies reported correspondent data; five in females [26,38–41] and four in males [35,38,39,42]. In female children, the pooled geometric mean titer estimates were: 7·1 against HPV6 (95% CI 6·79–7·41; I^2 = 96·6%, p < 0·0001), 7·32against HPV11 (95% CI 7·15–7·5; I^2 = 90·6%,

p < 0·0001), 8·71 against HPV16 (95% CI 8·52–8·91; I^2 = 90·2%, p < 0·0001), and 7·35 against HPV18 (95% CI 7·11–7·58; I^2 = 92·7%, p < 0·0001). In male children, the corresponding estimates were: 6·62 against HPV6 (95% CI 6·29–6·94; I^2 = 86·0%, p < 0·0001), 7·07against HPV11 (95% CI 6·90–7·23; I^2 = 63·1%, p < 0·0001), 8·53 against HPV16 (95% CI 8·28–8·78; I^2 = 73·0%, p < 0·0001), and 7·21 against HPV18 (95% CI 7·08–7·34; I^2 = 26·4%, p < 0·0001).

Results from meta-regression of immunogenicity data included all studies per virus type independently of age and sex. These analyses showed that age is the most significant factor affecting the geometric mean titer in both sexes (p < 0·0001) (Table 3). Regardless of age, females had significantly higher GMTs than males against HPV 6 (p = 0·022). Although 95% confidence intervals overlapped in the meta-analyses, females showed a tendency for higher titers than males for HPV 11 (p = 0·066) and and HPV18 (p = 0·079) (Table 3).

At least half of the studies did not report sufficient information to be able to exclude a potential bias regarding sequence generation of randomization, concealment of allocation, and blinding of participants and/or study personnel. Therefore, bias in these studies cannot be excluded (for details see Table 2). All but two studies were financed by pharmaceutical companies (Table 1).

4. Discussion

Despite the efficacy and safety of the HPV vaccines in preventing cervical cancer, many questions remain unanswered, especially

Table 1
Description of included studies.

Author(s)	Location	Design	Sex	Age	Funding Source
Castellsague 2011 [25]	Multicenter (7 countries)	RCT	Women	34.3 ± 6.3	Merck & Company, Inc.
Dobson 2013 [26]	Canada	RCT	Women Girls	19.3 ± 2.8 12.3 ± 1.4	Ministries of Health in the provinces of British Columbia, Nova Scotia, and Quebec
Ferris 2014 [38]	Multicenter (10 countries)	RCT	Girls Boys	11.9 ± 1.9	Merck & Company, Inc.
Hillman 2012 [33]	Multiple (18 countries)	RCT	Men	15–20 21–27	Merck & Company, Inc.
Kang 2008 [27]	Korea	RCT	Women Girls	9–23	Merck & Company, Inc.
Li 2012 [39]	China	RCT	Girls Boys	10–15 10–15	Merck & Company, Inc.
Lin 2014 [36]	USA	RCT	Men	21.4 ± 2.2	Merck & Company, Inc.
Mikamo 2019 [34]	Japan	RCT	Men	22.6 ± 2.1	Merck & Company, Inc.
Mugo 2015 [28]	Ghana, Kenya, Senegal	RCT	Women Girls	9–26	Merck & Company, Inc.
Murata 2019 [42]	Japan	RCT	Boys	12.2 ± 2	Merck & Company, Inc.
Neuzil 2011 [40	Vietnam	RCT	Girls	12.1 (10.8–4.2)	Bill & Melinda Gates Foundation
Pinto 2019 [37]	Multiple (USA, Mexico)	Clinical Trial	Men	38 (27–61)	Merck & Company, Inc.
Ruiz-Sternberg 2018 [29]	Multiple (18 countries)	Clinical Trial	Women	21.9 ± 2.5	Merck & Company, Inc.
Sudenga 2017 [30]	South Africa	RCT	Women	16–24	Merck & Company, Inc.
Tay 2008 [31]	Asia Pacific Non-Asia Pacific	Clinical Trial	Women	21 ± 5 20 ± 4	Merck & Company, Inc.
VanDamme 2016 [35]	Belgium, Germany, Netherlands	RCT	Men	16.4 ± 0.5 22.1 ± 2.3	Sanofi Pasteur MSD
Vesikari 2015 [41	Multiple (6 countries)	RCT	Girls	11 ± 1 14.3 ± 0.8	Sanofi Pasteur MSD
Villa 2005 [32]	Multiple	RCT	Women	20.2 ± 1.7	Merck & Company, Inc.

Table 2
Quality of included studies.

Author(s)	Design	Sequence Generation	Allocation Concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete data	Selective outcome reporting	Other sources of bias
Castellsague 2011	RCT	low	low	low	low	low	low	low
Dobson 2013	RCT	low	unclear	unclear	low	low	low	low
Ferris 2014	RCT	low	low	low	low	low	low	low
Hillman 2012	RCT	low	unclear	low	low	low	low	low
Kang 2008	RCT	unclear	unclear	unclear	unclear	low	low	low
Li 2012	RCT	unclear	unclear	unclear	unclear	low	low	low
Lin 2014	RCT	unclear	unclear	unclear	unclear	low	low	low
Mikamo 2019	RCT	low	low	low	low	low	low	low
Mugo 2015	RCT	unclear	unclear	unclear	unclear	low	low	low
Murata 2019	RCT	low	low	low	low	low	low	low
Neuzil 2011	RCT	Low	unclear	unclear	unclear	low	low	low
Pinto 2019	Clinical Trial							
Ruiz-Sternberg 2018	RCT	low	low	low	low	low	low	low
Sudenga 2017	RCT	unclear	unclear	low	low	low	low	low
Tay 2008	Clinical Trial							
VanDamme 2016	RCT	low	low	low	low	low	low	low
Vesikari 2015	RCT	low	low	low	low	low	low	low
Villa 2005	RCT	low	unclear	low	low	low	low	low

Table 3
Outcomes of meta-analyses of included studies.

Virus	Age class	Sex	N studies	Mean GMT (95% CI)	I^2 (%)
HPV6	children	f	5	7.1 (6.79–7.41)	96.6
		m	4	6.62 (6.29–6.94)	86.0
	adults	f	8	6.42 (6.21–6.62)	98.6
		m	4	6.20 (6.02–6.38)	92.7
HPV11	children	f	5	7.32 (7.15–7.5)	90.6
		m	4	7.07 (6.90–7.23)	63.1
	adults	f	8	6.60 (6.45–6.75)	97.2
		m	4	6.46 (6.25–6.67)	95.5
HPV16	children	f	5	8.71 (8.52–8.91)	90.2
		m	4	8.53 (8.28–8.78)	73.0
	adults	f	8	8.00 (7.85–8.16)	96.9
		m	5	7.89 (7.72–8.05)	92.3
HPV18	children	f	5	7.35 (7.11–7.58)	92.7
		m	4	7.21 (7.08–7.34)	26.4
	adults	f	8	6.42 (6.21–6.63)	98.3
		m	5	6.20 (5.96–6.44)	94.7

GMT = geometric mean titers, log-transformed.

regarding the difference in the vaccine's immunogenicity between the two sexes. To our knowledge, this is the first systematic review of the effect of sex on the immunogenicity of the quadrivalent HPV vaccine. Our results suggest that the qHPVV is more immunogenic in females than in males, and more immunogenic in children than in adults.

We found that females, regardless of age group, had higher titers after vaccination than males did. Although not confirmed for HPV vaccination, sex differences in humoral responses to viral vaccines have been reported often and many physiological explanations have been proposed [43]. The protective effect of the Bacillus Calmette-Guerin (BCG) vaccine in children (recommended in countries endemic with TB) was more marked in girls [44,45]. Stronger humoral responses in females were also found after the hepatitis B (HBV) vaccination [9,15,19]. A retrospective cohort found that in men and in elderly women, more than 5% of subjects did not respond properly to the HBV vaccine and showed a steeper decline in antibody titers [46]. Interestingly, HBV can also be transmitted sexually. Many biological mechanisms contributing to the sex difference in response to viral vaccines have been described. T-cells isolated from women exhibit higher cytotoxic activity than T-cells isolated from men [47], and females show greater antibody responses in general [9]. Sex hormones affect the function of immune cells in a dose-dependent manner [48]. While estrogens promote antibody production by B cells, androgens and progesterone inhibit antibody production by B cells [49]. Additionally, epigenetic and genetic factors affect the immune response to vaccines, as indicated by the immune response difference before puberty [14]. The X chromosome contains a large number of immune-related genes that are prone to damage and mutations. These mutations are more likely to be expressed in males since they have one copy only of the X chromosome, while females benefit from two copies that are unlikely to carry the same mutations [50]. Other than the general reasons for the sex difference in immunity, like sex hormones and chromosomes, that influence the immune response against all infectious diseases, there are specific differences between females and males that apply only to Sexually Transmitted Infections [14]. Many STIs are transmitted more efficiently from males to females. For example, the risk of genital herpes transmission from a male to a female partner is 19%, whereas it is 5% for transmission from female to her male partner [51]. After a single episode of sexual intercourse, a woman has a 60% to 90% chance of contracting gonorrhea from her infected male partner, whereas the risk for an uninfected male to get the infection from his female partner is 20% to 30% [52,53]. The reasons for this difference include greater exposure in females as a result of pooled semen in the vagina and greater trauma to the surfaces during intercourse. Most cases of tubal factor infertility are attributable to untreated sexually transmitted diseases that ascend along the reproductive tract and are capable of causing tubal inflammation, damage, and scarring [54]. In men, semen quality deteriorates with STIs [55]. These physiological and anatomical differences in susceptibility and consequences of STIs may have contributed to the evolution of sex-specific immune responses against these infection.

Secondly, we found that the sex difference in response to Low Risk (LR) strains of HPV tends to be stronger than it is to High Risk (HR) strains. Since the most detrimental outcomes of HPV infections are malignancies (cervical and oropharyngeal), we had expected the sex difference in response to the vaccine to be more pronounced against types 16 and 18 (high risk) than 6 and 11 (low risk). Interestingly, one study pointed out that HR HPV types use a stealth strategy in which the virus produces relatively few virions to delay the immune response [56]. Although this strategy reduces the probability of transmission during sexual contact, it enables the virus to persist for longer periods, which is usually a perquisite for causing cancer [57,58]. LR types, on the other hand, achieve higher transmission per sexual contact by producing larger numbers of virions [56,59]. In other words, LR strains follow a high-transmissibility, low-persistence strategy, while HR strains follow a low-transmissibility, high-persistence strategy. The difference in transcription rates and transmissibility between LR and HR strains may contribute to difference in the immune reactivity to these viruses between the sexes.

Among those considered, age was the most significant factor affecting the geometric mean titer after vaccination with qHPVV. In both sexes, GMTs were consistently higher in younger age groups than older groups. This observation is conformant with the existing literature on the efficacy and immunogenicity of the HPV vaccine. In one study, girls between 9 and 13 years of age who received a 2-dose schedule had 1·77- to 2·24-fold higher GMTs than women between 16 and 26 receiving a 3-dose schedule [60]. In fact, immunogenicity-bridging studies have established better immune responses in girls than in women [61]. CDC now recommends 2 doses of HPV vaccine instead of 3 in 11 or 12 year-old boys and girls [62]. Many explanations have been proposed for this difference in immune response between age groups. Generally, the immune response after receiving the vaccine is best if the receiver is naïve to the virus. Therefore, vaccination guidelines recommend vaccination at 11 or 12 (i.e., before sexual debut) but it can be started from age 9 [63].

This is the first systematic review comparing the immunogenicity of the quadrivalent HPV vaccine between the two sexes. One strength of this systematic review is that it was based on a compre-

hensive search strategy. The limitations arise, however, from the limitations of the primary studies included. The RCTs were designed to measure the efficacy and immunogenicity of the qHPV vaccine but not to compare the immunogenicity between the sexes. Therefore, many of them lack the power to make this comparison. Moreover, there are still too few studies on the immunogenicity of the HPV vaccine in men, which resulted in significantly larger confidence intervals, decreasing the ability to compare the results. In several studies it was not possible to clearly separate the groups in children and adults according to our definition (cut at 16 years of age), so that our results might be slightly blurred for some studies [27,28]. Furthermore, we focused on the immunogenicity at the seventh month even though the persistence of the antibodies in the long term is an important indicator of immunogenicity. We chose this time point because there are still too few studies that followed up GMTs in the long term. Even though our search protocol was comprehensive, and we used broad search terms, it remains possible that we might have missed some relevant studies.

None of the included studies had a high risk of bias. Nonetheless, the risk of bias was unclear in some. Particularly random sequence generating was often not explicitly described and therefore it was not possible to exclude any source of bias. Concealment of allocation and blinding of the personnel and outcome assessors were also not explicitly and clearly described in some trials. We could not, therefore, exclude the risk of bias in these studies.

HPV vaccination of girls, boys, and women has become standard in many countries, but several countries still do not vaccinate boys, and expanding the vaccination programs to include men is still a matter of discussion. This is particularly relevant to high-risk groups like men who have sex with men (MSM). Other than being at high-risk, this group does not directly benefit from herd immunity due to high coverage in females [64]. The sex-difference in the immunogenicity of the vaccine might be important for understanding potential differences in efficacy and side effect between male and females. This systematic review shows that the number of studies on the immunogenicity of the HPV vaccine in men is still small and data is still lacking, but existing studies show a difference in the immunogenicity of the qHPV vaccine between the two sexes. This indicates the need to conduct more clinical trials to bridge the gap between the two sexes. As very few studies show results in the long term by sex, indicating that the sex differences might persist at least for some viral types, more long-term studies might have an impact on immunization strategies [38,65]. In accordance with previous studies, age was a significant factor affecting vaccine efficacy and we support recommendations for early vaccination of girls and boys. We also stress the importance of clearly describing the randomization and blinding protocols in publications to exclude any possible sources of bias.

5. Contributors

LA, NB, and FR designed the study. LA and VMH extracted the data, NB performed the meta-analysis, and FR supervised the project. LA wrote the first draft and all authors commented on several drafts of the manuscript and approved the final version. All authors contributed intellectually to the work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.02.022.

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